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FRONTIER

Targeted therapies in gastric cancer and future perspectives

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Abstract

Advanced gastric cancer (AGC) is associated with a high mortality rate and, despite multiple new chemotherapy options, the survival rates of patients with AGC remains poor. After the discovery of targeted therapies, research has focused on the new treatment options for AGC. In the last two decades, many targeted molecules were developed against AGC. Currently, two targeted therapy molecules have been approved for patients with AGC. In 2010, trastuzumab was the first molecule shown to improve survival in patients with HER2-positive AGC as part of a first-line combination regimen. In 2014, ramucirumab was the second targeted molecule to improve survival rates and was suggested as treatment for patients with AGC who had progressed after first-line platinum plus fluoropyrimidine with or without anthracycline chemotherapy. Ramucirumab was the first targeted therapy acting as a single agent in patients with advanced gastroesophageal cancers. Although these two molecules were introduced into clinical use, many other promising molecules have been tested in phase Ⅰ-Ⅱ trials. It is obvious that in the near future many different targeted therapies will be in use for treatment of AGC. In this review, the current status of targeted therapies in the treatment of AGC and gastroesophageal junction tumors, including HER (2-3) inhibitors, epidermal growth factor receptor inhibitors, tyrosine kinase inhibitors, antiangiogenic agents, c-MET inhibitors, mammalian target of rapamycin inhibitors, agents against other molecular pathways fibroblast growth factor, Claudins, insulin-like growth factor, heat shock proteins, and immunotherapy, will be discussed.

Key words: Targeted therapies; Antibodies; Gastric cancer; Tyrosine kinase; Survival

Core tip: Trastuzumab was the first molecule shown to prolong both progression-free survival and overall survival in patients with advanced gastric cancer (AGC) when added to first-line chemotherapy in patients with AGC. In 2014, ramucirumab was approved as a single agent or in combination with paclitaxel for the treatment of patients with AGC. Many phase Ⅱ-Ⅲ clinical trials failed to showed activity of different targeted agents in patients with AGC. On the other hand, some molecules have shown promising activity in phase Ⅱ trials and are expected to be in use in the coming years. Pertuzumab and c-Met pathway inhibitors have shown modest activity in a phase Ⅱ trial. The results of two important ongoing phase Ⅲ trials (JACOB and RILOMET-1) may change the recommendations for first-line treatment options in patients with AGC.

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INTRODUCTION

Gastric cancer is the second leading cause of cancer-related mortality worldwide, and its incidence is still increasing in developing countries[1]. Surgery is the curative treatment in the early stages of gastric cancer. However, the majority of patients with gastric cancer are diagnosed in the advanced stage in which curative treatment approaches are not possible[2]. In patients with advanced disease, chemotherapy improves the overall survival (OS) and progression-free survival (PFS) rates compared with best supportive care[3]. New chemotherapeutic agents have improved the response rates compared with previous chemotherapy regimens[4]. However, despite these new chemotherapy regimens, the 5-year survival rates of patients with advanced gastric cancer (AGC) are still only 20%-30%. Therefore, in recent years, research has focused on new treatment approaches for gastric cancer. In order to develop new molecules for gastric cancer treatment, it is very important to define the molecular pathways involved in the carcinogenesis of gastric cancer. A better understanding of molecular pathways that lead to cell growth, angiogenesis, and inhibition of apoptosis, will lead to new ideas for novel targeted therapies. In the last two decades, different molecules targeting different pathways were developed for the treatment of gastric cancer. In 2010, trastuzumab was the first molecule demonstrated to improve OS and PFS in patients with HER2-positive AGC[5]. Recently, ramucirumab was the second targeted molecule suggested for the treatment of AGC[6]. In addition to these two molecules, new targets and targeted therapies have been investigated. It is apparent that in the near future many different targeted therapies will be in use for the treatment of AGC. Accordingly, this review will focus on the current status of the available targeted therapies, and the therapies under investigation for the treatment of AGC.

EPIDERMAL GROWTH FACTOR RECEPTOR SIGNALING PATHWAY INHIBITORS

Epidermal growth factor receptor (EGFR) is a cluster of receptors, including human EGFR (HER)-1, HER2, HER3 and HER4. EGFR is located on the outside of cellular membranes and is activated by binding of specific ligands. Stimulation of EGFR leads to cell proliferation and differentiation[7]. The ligand binding to the extracellular part of the receptor, homodimerization and heterodimerization occurs, resulting in phosphorylation of intracellular tyrosine kinase (TK), and phosphorylated TK activation of intracellular protein kinases[8]. All these activated intracellular pathways result in cell cycle progression, apoptosis, proliferation, angiogenesis, and metastasis[9]. EGFR overexpression was detected in 30%-50% of patients with gastric cancers, and was associated with poor prognosis and shorter OS[10]. Molecules which block different parts of the EGFR signaling cascade have been tested in clinical trials. These molecules can be divided into two groups, namely monoclonal antibodies that block EGFR, and TK inhibitors.

Monoclonal antibodies against EGFR subtypes

Anti-HER 2 monoclonal antibodies: HER2 is a transmembrane TK receptor with the potential to heterodimerize with HER1, HER3, or HER4. In HER2-positive tumors, the dimerization of HER2 with HER3 is an important process initiating oncogenic transformation[11]. Overexpression of HER2 is a marker of poor prognosis, and is associated with a high relapse rate in patients with breast cancer[12]. However, in gastric cancer patients, the prognostic value of amplified HER2 is controversial. A small study reported that in gastric cancer, HER2 overexpression or amplification significantly improved prognosis[13]. On the other hand, a systematic data analysis of the literature suggested a potential role for HER2 as a negative prognostic factor[14].

Trastuzumab is a monoclonal antibody against the HER2 extracellular domain. In the randomized phase Ⅲ ToGA trial in patients with AGC, the addition of trastuzumab to first-line chemotherapy improved OS and PFS compared with chemotherapy alone[5]. In the ToGA trial, 3665 patients with AGC were screened for their HER2 amplification status using immunohistochemistry (IHC) and fluorescence *in situ* hybridization (FISH). Of them, 594 had a +3

staining score on IHC or were FISH-positive (HER2: CEP17 ratio ⩾ 2). These patients were randomly assigned to receive chemotherapy plus trastuzumab or chemotherapy alone. The patients received capecitabine combined with cisplatin or cisplatin combined with fluorouracil as a chemotherapy regimen. The proportion of HER2 positivity was 22.1%. Median OS was 13.8 mo (95%CI: 12-16) in patients receiving trastuzumab and chemotherapy compared to 11.1 mo (95%CI: 10-13) in patients receiving chemotherapy alone, and the difference was statistically significant (HR = 0.74; 95%CI: 0.60-0.91, *P* = 0.0046). In a *post hoc* analysis of the ToGA trial, the OS of patients with high HER2 expression (IHC2+ and FISH positive or IHC3+; *n* = 446) who received trastuzumab was 16·0 mo (95%CI: 15-19) compared with 11.8 mo (95%CI: 10-13) in patients receiving chemotherapy alone (HR = 0.65; 95%CI: 0.51-0.83, *P* = 0.036). Median PFS was also significantly improved in the trastuzumab plus chemotherapy arm compared with chemotherapy alone (median PFS: 6.7 mo *vs* 5.5 mo, HR = 0.71; 95%CI: 0.59-0.85, *P* = 0.0002). All grades of adverse events and serious adverse events (grade 3 or 4) were similar between the two groups. It was previously noted that trastuzumab might cause significant cardiac toxicity. However, in this trial, cardiac toxicity was rare and rates of cardiac events were similar between the trastuzumab plus chemotherapy and chemotherapy alone groups [17 (6%) *vs* 18 (6%)]. After the impressive results of the ToGA trial, trastuzumab in combination with cisplatin and a fluoropyrimidine (fluorouracil or capecitabine) was suggested as category 1 first-line therapy in patients with HER2 overexpressed AGC (National Comprehensive Cancer Network, European Society of Medical Oncology Guidelines). In 2010, the Food and Drug Administration, and European Medicine Agency approved trastuzumab in combination with chemotherapy for use in HER2-overexpressed AGC patients.

In a study presented at the American Society of Clinical Oncology (ASCO) Meeting 2013, trastzumab-naive patients with AGC were treated with trastzumab in combination with paxlitaxel. Forty six patients were enrolled and received paclitaxel (80 mg/m^2 on days 1, 8, and, 15 q4w) plus trastuzumab (8 mg/kg initial dose, followed by 6 mg/kg, every 3 wk). The overall response rate (ORR) was 37.2% (95%CI: 23.0%-53.3%). Median PFS was 5.2 mo (95%CI: 3.9-6.6). The combination of trastuzumab with paxlitaxel as second-line therapy showed efficacy in AGC patients[15].

In the phase Ⅱ NEOHX study, perioperative chemotherapy treatment with trastuzumab in combination with capecitabine and oxaliplatin was evaluated in patients with HER2-positive resectable gastric cancer. This combination regimen was administered as 3 cycles in the preoperative and postoperative period. Thirty six patients were enrolled. Three patiens had a pathological complete response (8.3%; 95%CI: 2%-22%). The disease-free survival at 18 and 24 mo was 71% (95%CI: 53%-83%) and 60%, respectively. Perioperative trastuzumab plus capecitabin/oxaliplatin showed promising efficacy[16] (Tables 1 and 2).

In 2011, Begnami and colleagues explored the gene and protein expression of the HER family in 221 patients with GC and analyzed the correlation between clinicopathological parameters. This report showed that HER2 and HER3 overexpression was associated with poor prognosis[17]. In a HER2-positive human gastric cancer xenograft Mouse models, pertuzumab in combination with trastuzumab was showed significant anti-tumor activity compared to each mono therapy[18]. Pertuzumab is a recombinant humanized monoclonal antibody that binds to the extracellular dimerization domain of HER2 and prevents heterodimerization of HER2 with the EGFR, HER3, and HER4[19]. In a phase Ⅲ trial, it was demonstrated that pertuzumab in combination with trastuzumab improved OS in patients with advanced breast cancer[20]. In a phase Ⅱ trial, pertuzumab and trastuzumab in combination with chemotherapy produced a partial response in 85% after 6 cycles of therapy in patients with AGC[21]. At the ASCO Meeting, the schema of ongoing randomized phase Ⅲ trial of pertuzumab and trastzuzumab in combination with chemotherapy as first-line therapy in patients with advanced gastric or gastroesophageal junction cancer was presented. In this study, HER2 amplified AGC or advanced gastroesophageal cancer patients were randomized 1:1 to arm A: pertuzumab + trastuzumab + cisplatin + fluoropyrimidine or arm B: placebo + trastuzumab + cisplatin + fluoropyrimidine. The primary end point of this study is OS, and 780 patients will be enrolled from 33 countries. The results of this study are awaited by clinicians[22].

In gastric cell lines, binding of trastuzumab emtansine (T-DM1) to the cell surface HER2 was significantly increased by pertuzumab. Concomitant administration of peruzumab with T-DM-1 blocks HER3 and down-stream TK pathways. The combination of two anti-HER enhanced their activity and this may be a promising anti-tumor combination against HER2-positive gastric cancer[23].

T-DM1 is a HER2 targeted antibody drug conjugate, composed of trastuzumab conjugated with a potent cytotoxic agent DM1 (derivative of maytansine). T-DM1 was designed to increase the efficacy of trastuzumab. T-DM1 binds to the extracellular domain of HER2 and is internalized into the tumor cell, then the antimicrotubule agent emtasine is relaesed[24]. The efficacy of T-DM1 was demonstrated in HER2-positive metastatic breast cancer patients[25]. In Her2-positive xenograft mouse models, T-DM1 in combination with pertuzumab showed significant antitumor activity compared with single agent therapies[26].

In a phase Ⅰ trial, TD-1 in combination with capecitabine was tested in patients with advanced gastric or breast cancer. Of the six patients who received

Table 1 Completed randomized Phase Ⅱ and Phase Ⅲ trials

Target	Agents	Name of trial and setting	Phase	Number of patients	PFS (mo)	*P* value	OS (mo)	*P* value	Results
HER-2	Fluoropyrimide/cisplain + Trastuzumab *vs* Fluoropyrimide/cisplain	ToGA, First line	Ⅲ	594	6.7 *vs* 5.5	< 0.001	13.8 *vs* 11.1	0.004	PFS and OS was improved
HER-2	Lapatinib plus once-per-week paclitaxel *vs* paclitaxel	TYTAN, Second line	Ⅲ	261	5.4 *vs* 4.4	0.850	11.0 *vs* 8.9	0.104	No effect on PFS and OS
HER-2	Cap/Ox plus lapatinib or Cap/Ox plus placebo	LOGiC, First line	Ⅲ	545	6.0 *vs* 5.4	0.100	12.2 *vs* 10.5	0.350	No effect on PFS and OS
EGFR	Cisplatin and capecitabine + cetuximab *vs* cisplatin and capecitabine	EXPAND, First line	Ⅲ	904	4.4 *vs* 5.6	0.320	9.4 *vs* 10.7	0.950	No effect on PFS and OS
EGFR	mEOC plus panitumumab *vs* EOC	REAL, First line	Ⅲ	553	6.0 *vs* 7.4	0.068	8.8 *vs* 11.3	0.013	No effect on PFS and OS
VEGF	Bevacizumab plus cisp/cape/fluorouracil *vs* plc plus cisplatin/capecitabine/fluorouracil	AVAGAST, First line	Ⅲ	774	6.7 *vs* 5.3	0.003	12.1 *vs* 10.1	0.100	PFS was improved, No effect on OS
VEGF	Ramucirumab *vs* placebo	REGARD, Second line	Ⅲ	355	2.1 *vs* 1.3	< 0.001	5.2 *vs* 3.8	0.047	PFS and OS was improved
VEGF	Ramucirumab plus paclitaxel *vs* placebo plus paclitaxel	RAINBOW, Second line	Ⅲ	665	4.4 *vs* 2.9	< 0.001	9.6 *vs* 7.4	0.017	PFS and OS was improved
VEGF	Apatinib 850 mg *vs* apatinib 425 *vs* placebo	NN, Third line	Ⅱ	144	3.67 *vs* 3.20 *vs* 1.40	< 0.001	4.83 *vs* 4.27 *vs* 2.50	< 0.001	PFS and OS was improved
MET	Rilotumumab 15 mg/kg per rilotumumab 7.5 mg/kg, or placebo plus ECX	NN, First line	Ⅱ	121	5.1 *vs* 6.8 *vs* 4.2	0.016	9.7 *vs* 11.1 *vs* 8.9	0.100	PFS and OS was improved
m-TOR	Everolimus 10 mg *vs* placebo	GRANITE, ≥ Second line	Ⅲ	656	1.7 *vs* 1.4	0.780	5.4 *vs* 4.3	0.124	No effect on PFS and OS

Plc: Placebo; mEOC: Modified epirubicin, oxaliplatin and capecitabine; DCF: Docetaxel, cisplatin, 5-fluorouracil; ECF/ECX: Epirubicin, cisplatin, fluorouracil/capecitabine; EGFR: Epidermal Growth Factor Receptor; VEGF: Vascular Endothelial Growth Factor; ECX: Epirubicin, cisplatin, capecitabine; NN: No specific study name was defined; OS: Overal survival; PFS: Progression free survival.

Table 2 Finished Phase Ⅱ studies

Target	Agents	Name of Trial and Setting	Phase	Number of patients	PFS (mo)	OS (mo)	Results
HER-2	Lapatinib	S0413, First line	Ⅱ	47	1.9	4.8	Positive
HER-2	Lapatinib plus ECF or ECX *vs* placebo plus ECF or ECX	EORTC 40071, First line	Ⅱ	28	7.1 *vs* 5.9	13.8 *vs* 10.1	Negative[1]
HER-2	MK-2206 (AKT inhibitor)	S1005, Second line	Ⅱ	70	1.8	5.1	Negative
Pan-HER	Saracatinib (Src inhibitor)	NN, ≥ Second line	Ⅱ	21	1.8	7.8	Negative
Pan-HER	Dacomitinib	NN, ≥ Second line	Ⅱ	27	2.1	7.1	Positive
EGFR	Cetuximab plus mFOLFOX6	NN, First line	Ⅱ	40	5.5	9.9	Positive
EGFR	Cetuximab plus FOLFIRI	NN, First line	Ⅱ	49	9.0	16.5	Positive
EGFR	Panitumumab with dose dense DCF	NN, First line	Ⅱ	52	4.8	9.4	Positive
VEGF	Bevacizumab plus irinotecan and cisplatin	NN, First line	Ⅱ	47	8.3	12.3	Positive
VEGF	Bevacizumab plus docetaxel/oxaliplatin	NN, First line	Ⅱ	38	6.6	11.1	Positive
m-TOR	Everolimus 10 mg	NN, ≥ Second line	Ⅱ	53	2.7	10.1	Positive

[1]Early terminated. VEGF: Vascular endothelial growth factor; m-TOR: Mammalian target of rapamycin; NN: No specific study name was defined.

capecitabine 750 mg/m^2 and T-DM1 3.6 mg/kg every 3 wk, four had parital and one had stable disease[27].

An ongoing phase Ⅱ/Ⅲ study (NCT01641939) will evaluate the efficacy of T-DM1 in patients with HER2-overexpressed AGC. In this study, T-DM1 will be compared with taxane chemotherapy alone. The patients will be randomized into three different groups as arm a: 3.6 mg/kg T-DM1 every 3 wk; arm b: 2.4 mg/kg T-DM1 every week; and arm c: standard taxane therapy (paclitaxel 80 mg/m^2 per week or docetaxel 75 mg/m^2 q3wk). The primary outcomes of the study are effective dose of T-DM1, and OS. The planned final data collection date is December 2016[28] (Figure 1).

Anti-HER3 monoclonal antibody: HER 3 is normally expressed in various tissues including gastrointestinal, urinary, respiratory, and reproductive tracts[29]. In tumor tissues the overexpression of HER3 is frequently accompanied by overexpression of EGFR and/or

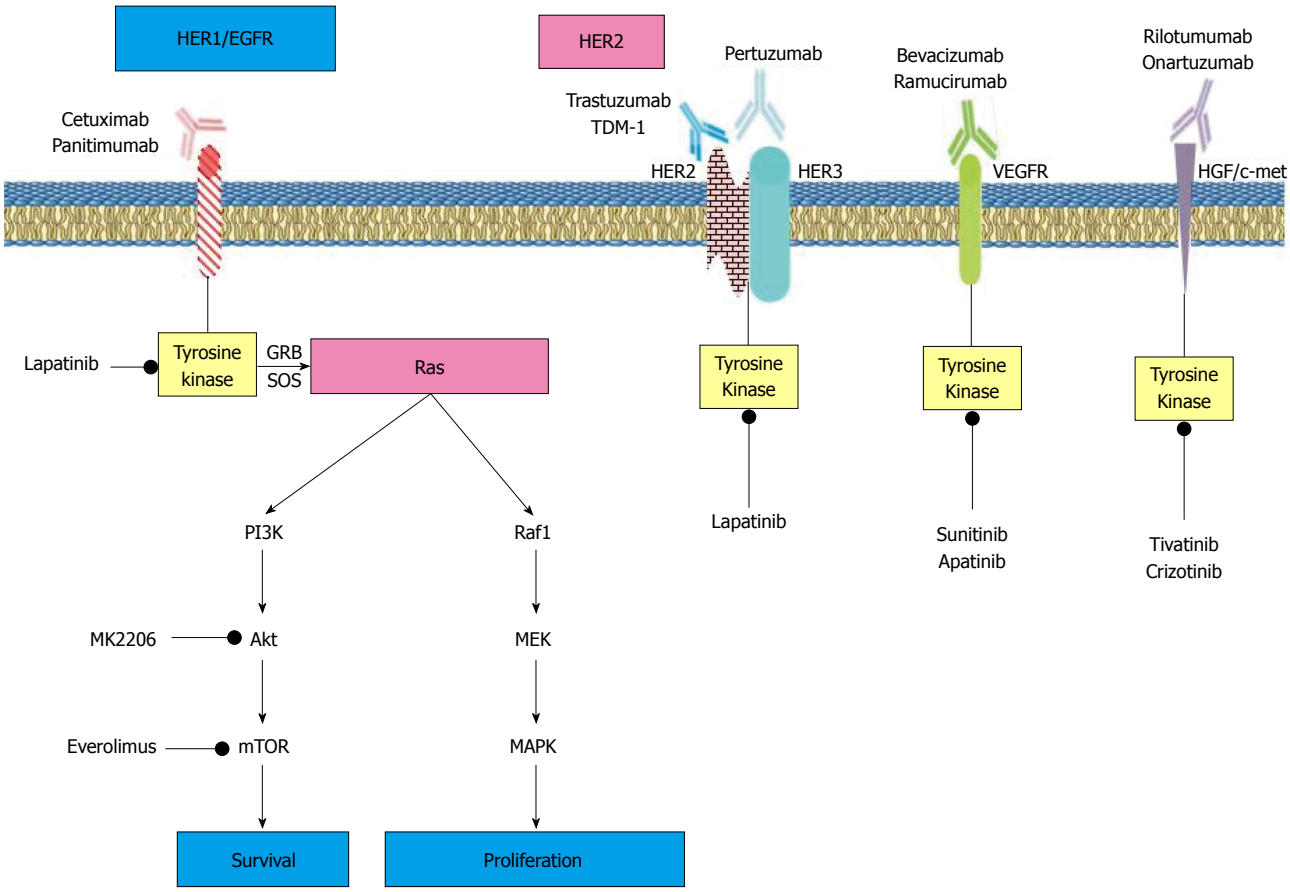

Figure 1 Schematic view of targeted therapies in gastric cancer and sites of action. EGFR: Epidermal growth factor receptor; VEGFR: Vascular endothelial growth factor receptor; HGF: Hepatocyte growth factor; PI3K: Phosphatidylinositol 3-kinase; Akt: Protein kinase B; mTOR: Mammalian target of rapamycin; MAPK/MEK: Mitogen-activated protein kinases; Raf1: Serine/Threonine-Specific Protein Kinases; SOS: Small guanosine triphosphatases (GTPases); GRB2: Growth factor receptor-bound protein 2.

HER2[30]. HER3 has clinical significance in patients with gastric cancer. In a preclinical study evaluating the HER3 status of surgical specimens of 191 patients with gastric cancer, HER 3 positivity was associated with poor OS (P = 0.035)[17].

In HER2-positive tumors, Her2 hetorodimerizes with HER3 and promotes tumor progression[11]. In gastric cancer, HER3 overexpression was associated with poor prognosis and unfavorable survival[31]. In a phase Ⅰ trial, LJM716 (fully human anti-HER3 monoclonal antibody) in combination with trastuzumab was evaluated in patients with HER2-positive metastatic breast or gastric cancer who had progressed on previous HER2-directed therapy. Of 30 evaluable patients, a partial response and stable disease was obtained in 2 and 12 (40%) patients with advanced breast or gastric cancer. The most frequent treatment-related adverse events (all grades) were diarrhea (91%), nausea (29%), fatigue (23%), and chills (20%). LJM716 is the first anti-HER3 monoclonal antibody reported to demonstrate clinical efficacy in combination with trastuzumab in trastuzumab-resistant patients[32].

MM-111 is a bispecific antibody targeting HER3, and forms a trimeric complex with HER2 and HER3. In a phase 1 trial, MM-111 in combination with five different chemotherapy regimens was tested in 86 patients with advanced cancer (11 bladder, 46 breast, 15 gastroesophageal, 14 other cancers). A partial response and stable disease were observed in 19 and 28 patients, respectively[33]. In an ongoing randomized phase Ⅱ trial in patients with advanced gastric or esophageal cancer, MM-111 combined with paxlitaxel and trastuzumab is being evaluated as second-line therapy[34].

Anti-EGFR/HER1 monoclonal antibodies: Cetuximab is a chimeric monoclonal recombinant antibody binding to the extracellular domain of EGFR/HER1[35]. In a phase Ⅱ trial, cetuximab was combined with the mFOLFOX6 regimen as first-line therapy in patients with metastatic gastric cancer. Patients received cetuximab 400 mg/m^2 at week 1 and 250 mg/m^2 weekly thereafter until disease progression and biweekly mFOLFOX6 (oxaliplatin 100 mg/m^2, leucoverin 100 mg/m^2, bolus fluorouracil followed by 46-h infusion of 2400 mg/m^2) regimen. In this study, response rate was 50.0% (95%CI: 34.1%-65.9%) and median OS was 9.9 mo[36]. In another phase Ⅱ trial, cetuximab was combined with irinotecan/leucoverin and fluorouracil as first-line treatment in

patients with AGC. The response rate was 46% and disease control rate was 79%. The authors reported that the median PFS was 9.0 mo (95%CI: 7.1-15.6) and OS was 16.5 mo (95%CI: 11.7-30.1)[37]. In 2010, another phase Ⅱ trial from Germany evaluated the efficacy of weekly cetuximab in combination with oxaliplatin 50 mg/m^2, 5-FU 2000 mg/m^2, and folinic acid 200 mg/m^2 on days 1, 8, 15, and 22, in patients with metastatic gastric cancer. In this trial, median PFS was 7.6 mo (95%CI: 5.0-10.1 mo) and median OS was 9.5 mo (95%CI: 7.9-11.1 mo) with a reported response rate of 65% (95%CI: 50%-79%)[38]. One more phase Ⅱ trial tested the efficacy of cetuximab in combination with XELOX in patients with AGC. Similar to other studies, the response rate was 52.3% and median PFS and OS were 6.5 mo (95%CI: 4.9-8.4) and 11.8 mo (95%CI: 6.7-16.8), respectively[39]. In a randomized phase Ⅲ trial, cetuximab was added to cisplatin and capecitabine and compared with chemotherapy alone in patients with AGC. The primary endpoint of the study was PFS. The median PFS of 455 patients receiving cetuximab plus chemotherapy was 4.4 mo (95%CI: 4.2-5.5) compared with 5.6 mo (5.1-5.7) in 449 patients who were given chemotherapy alone (HR = 1.09; 95%CI: 0.92-1.29, *P* = 0.32). In the cetuximab plus chemotherapy and chemotherapy alone groups, OS was 9.4 mo and 10.7 mo, respectively (*P* = 0.95). In this randomized phase Ⅲ trial, the addition of cetuximab to chemotherapy showed no additional benefit[40].

Panitumumab is a humanized, immunoglobulin G2 monoclonal antibody against the EGFR/HER1 extracellular domain[41]. In phase Ⅱ trials, blocking the EGFR1 pathway resulted in high efficacy and improved PFS and OS[42]. Therefore, following the dose finding study of panitumumab in patients with AGC, the phase Ⅲ REAL trial was conducted.

In a phase Ⅲ trial, the efficacy of adding panitumumab to combined chemotherapy was tested in patients with advanced gastroesophageal carcinomas. In this trial, 553 patients were randomly assigned to receive standard dose EOC (epirubicin 50 mg/m^2, oxaliplatin 130 mg/m^2, and capecitabine 1250 mg/m^2) or modified-dose EOC plus panitumumab (mEOC + P; epirubicin 50 mg/m^2 and oxaliplatin 100 mg/m^2 on day 1, capecitabine 1000 mg/m^2 per day on days 1-21, and panitumumab 9 mg/kg on day 1). The primary endpoint of the study was OS. The median OS was 11·3 mo (95%CI: 9.6-13.0) in patients who received standard dose EOC compared with 8·8 mo (7.7-9.8) in patients who received panitumumab plus mEOC (HR = 1.37; 95%CI: 1.07-1.76, *P* = 0.013). In the standard dose EOC group, median PFS was 7.4 mo (6.3-8.5) compared with 6.0 mo (95%CI: 5.5-6.5) in the mEOC + P group (HR = 1.22; 95%CI: 0.98-1.52, *P* = 0.068). In the panitumumab plus EOC group, grade 3-4 adverse events such as diarrhea, mucositis, rash, and hypomagnesaemia were more frequent than in the EOC group. This trial concluded that adding panitumumab to chemotherapy in patients with advanced gasrtoesophageal cancer did not increase OS and was not recommended for clinical use[43]. In a recent phase Ⅱ trial, panitumumab in combination with dose dense docetaxel/cisplatin/fluorouracil chemotherapy regimen was given as first-line treatment to 52 HER2-negative patients with advanced gastric or gastroesophageal junction tumors. Complete, partial, and stable responses was observed in 3, 29, and 10 patients, respectively. Progression occurred in eight patients. The overall response rate was 62% (95%CI: 48-75). Median PFS and OS were 4.8 mo (95%CI: 4.1-6.9) and 9.4 mo (95%CI: 7.4-11.6), respectively. Panitumumab in combination with dose dense docetaxel/cisplatin/fluorouracil (DCF) showed a high efficacy rate. This combination was suggested to be evaluated in a neoadjuvant setting[44] (Figure 1).

EGFR FAMILY TYROSINE KINASE INHIBITORS

HER-2 TK inhibitors

In an EGFR-positive cell line, inhibition of TK domains produced a good antiproliferative effect[45]. Following studies which showed improved OS after blocking HER2 in patients with AGC, researchers targeted the intracellular TK domains of these receptors. The first molecule evaluated in patients with gastric cancer was lapatinib. It is a small dual TK inhibitor blocking both EGFR/HER1 and HER2 TK domains by binding to the adenosine triphosphate (ATP) binding site of the receptor's intracellular domain[46]. Lapatinib showed moderate activity in combination with capecitabine in patients with HER2-positive metastatic breast cancer[47]. In a phase Ⅱ trial, lapatinib as a single agent showed modest activity in patients with AGC, with median OS of 4.8 mo (3.2-7.4)[48]. Then, the phase Ⅲ TYTAN trial was conducted. In this trial, 261 patients identified as HER2-positive by FISH were randomized to receive lapatinib 1500 mg once daily plus once weekly paclitaxel 80 mg/m^2 or paclitaxel alone as second-line treatment. The primary endpoint of the study was OS. Secondary endpoints were PFS, time to progression (TTP), ORR, time to response, response duration, and safety. In the lapatinib plus paclitaxel group, median OS was 11 mo (95%CI: 9.5-14.5) compared with 8.9 mo (95%CI: 7.4-11.1) in the paclitaxel alone group (HR = 0.84; 95%CI: 0.64-1.11, *P* = 0.10). In the lapatinib plus paclitaxel group, median PFS was 5.4 mo (95%CI: 3.9-5.7) compared with 4.4 mo (95%CI: 3.7-5.6) in the paclitaxel alone group (HR = 0.85; 95%CI: 0.63-1.13, *P* = 0.2441). The ORR was higher in patients receiving lapatinib plus paclitaxel compared with patients receiving paclitaxel alone (OR = 3.85, *P* < 0.001). Similar rates of adverse events were detected in both treatment arms. Lapatinib plus paclitaxel showed activity in the second-line setting treatment of advanced stage gastric cancer

but it did not improve OS[49].

In a phase Ⅲ trial, the efficacy of lapatinib in combination with a capecitabine/oxaliplatin (CapeOx) chemotherapy regimen in patients with HER2-positive AGC was evaluated. A total of 545 patients were randomized to CapeOx every 3 wk (oxaliplatin 130 mg/m^2 day 1; capecitabine 850 mg/m^2 BID days 1-14), and daily laptinib (1250 mg) (CapeOx + Lapatinib) or placebo (CapeOx + Placebo). The primary endpoint was OS. In the lapatinib plus chemotherapy and chemotherapy alone groups, median OS was 12.2 and 10.5 mo, respectively (HR = 0.91; 95%CI: 0.73-1.12, P = 0.35). In the lapatinib and chemotherapy alone group, the objective response rate was 53% and 40%, respectively. In subgroup analyses, improvement in OS was detected in Asian patients (HR = 0.68) and those under 60 years (HR = 0.69). Skin toxicity and diarrhea were significantly higher in patients receiving lapatinib compared with chemotherapy alone. The addition of lapatinib to chemotherapy in patients with AGC did not improve OS. It has clinical activity in some specified subpopulations[50].

In 2015, lapatinib in combination with epirubicin, cisplatin, and fluorouracil (ECF)/capecitabine as first-line therapy in metastatic gastric cancer was evaluated. Twenty eight patients were enrolled. The median PFS was 7.1 mo with lapatinib *vs* 5.9 mo with chemotherapy alone (HR = 0.94; 95%CI: 0.41-2.14). In patients with AGC, lapatinib did not show activity in combination with ECF[51] (Tables 1 and 2).

Pan-HER family TK inhibitor

Activated HER2 forms heterodimers with HER3 and HER4, and the signals produced by the heterodimers activate intracellular TK pathways leading to tumor progression. Dacomitinib (PF00299804) is an irreversible pan-HER inhibitor *in vitro* and in *in vivo* models of gastric cancer. In preclinical studies, dacomitinib induced apoptosis in gastric cell lines[52]. In a phase Ⅱ trial including patients with HER2-positive AGC, after failure of at least one prior chemotherapy regimen, the efficacy of dacomitinib was investigated. A total of 27 patients were enrolled. Dacomitinib was administered orally once daily (45 mg/d) continuously for 21 d every 4 wk. The median PFS was 2.1 mo (95%CI: 2.3-3.4). The median OS was 7.1 mo (95%CI: 4.4-9.8). A PR was observed in two patients and stable disease in nine patients. The objective response rate was 7.4% (95%CI: 0%-17.5%) and disease control rate was 40.7% (95%CI: 21.9%-59.6%). This study concluded that dacomitinib is effective and safe in patients with HER2-positive gastric tumors[53].

AKT inhibitor

In HER2-positive malignancies, AKT (protein kinase B), which is a serine-threonine kinase, play a pivotal role during the transduction of activated HER2 signals, resulting in tumor cell survival and progression of tumors[54]. In patients with HER2-positive malignancies, AKT inhibitors may have potential therapeutic effects. In a phase Ib study, 17 patients (11 breast, 3 gastric, 1 esophageal cancer) with HER2-positive solid malignancies were enrolled. The AKT inhibitor MK2206 in combination with weekly paclitaxel 80 mg/m^2 and trastuzumab 2 mg/kg was tested. Fourteen patients were evaluable for tumor response and two patients had a complete response, seven had a partial response, and four were stable. The most common grade 3/4 side effects were neutropenia (6 patients), febrile neutropenia (1 patient), peripheral neuropathy (1 patient), and depression (1 patient)[55]. Afterwards a phase Ⅱ trial of MK2206 was performed in patients with metastatic gastric or gastroesophageal junction tumors as second-line therapy. Seventy patients were evaluated. The median PFS and OS were 1.8 mo (95%CI: 1.7-1.8 mo) and 5.1 mo (95%CI: 3.7-9.4 mo), respectively. The response rate was 1%. MK2206 has no beneficial activity in patients with advanced gastroesophageal cancers[56].

EGFR-dependent TK inhibitors

Src is a TK protein belonging to a family of non-receptor protein TKs (SFK). The activity of Src protein kinases are increased in epithelial human cancers[57]. The mitogenic signaling of activated EGFR works in a synergistic manner with Src TK, and activated EGFR ligand requires functional Src family kinases to transmit mitogenic responses[58]. Src is involved in EGFR pathways triggering cell proliferation, adhesion, invasion, migration, metastasis, and tumorigenesis[59]. It has been reported that the expression and/or activation of the Src family of protein kinases is increased in gastric cell lines[60]. In a study by Green *et al*[61], saracatinib (AZD0530), which is a small potent orally administered molecule inhibiting Src kinase activity by binding to ATP binding sites of Src kinases, inhibited tumor progression in a murine model of bladder cancer. In a phase Ⅱ trial, 21 patients with locally advanced or metastatic gastric or gastroesophageal junction tumors received saracatinib 175 mg/d in a 28-d cycle until progression. In this study, patients received a median of two cycles (range, 1-10) of therapy. No objective response was seen in 17 evaluable patients. Three patients had stable disease and 13 progressive disease. Median OS was 7.8 mo (95%CI: 3.9-12.2 mo) and PFS was 1.8 mo (95%CI: 1.5-1.9 mo). Most serious side effects of saracatinib treatment were fatigue (2 patients), hypoxia (2), anemia (3), and lymphopenia (2). In this phase Ⅱ trial, single agent saracatinib had no effect in first-line therapy of patients with advanced gastroesophageal cancer[62] (Figure 1)

VASCULAR ENDOTHELIAL SIGNALING PATHWAY INHIBITORS

Angiogenesis is one of the important steps of tumor growth, metastasis and progression[63]. Vascular endothelial growth factor (VEGF) is the key regulator of angiogenesis. The VEGF family has six members and the most widely defined is VEGF-A. In one study, specimens of 124 gastric cancers were evaluated, and an increased rate of hepatic metastasis, lymph node metastasis, and poor prognosis was associated with an increased number of microvessels in these specimens[64]. Maehara *et al*[65] reported that VEGF overexpression was associated with metastasis and poor prognosis. Based on these data, angiogenesis inhibitor molecules were evaluated in patients with AGC.

Anti-VEGF monoclonal antibody

Bevacizumab is the humanized monoclonal antibody targeting VEGF-A. Experimental studies showed that bevacizumab blocked all isoforms of VEGF-A and VEGF-A-dependent angiogenesis[66]. In many different solid organ cancer cell line studies, bevacizumab inhibited tumor growth as a single agent, and also in combination with doxorubicin, topotecan, paclitaxel, docetaxel, or radiotherapy resulting in additive or synergistic effects[67]. In 2006, a phase Ⅱ study of bevcizumab in combination with chemotherapy in the treatment of advanced gastroesophageal carcinoma was reported[68]. In this study, 47 patients with advanced gastroesophageal cancer were treated with bevacizumab 15 mg/kg on day 1, irinotecan 65 mg/m^2, and cisplatin 30 mg/m^2 on days 1 and 8, every 21 d. The primary endpoint was improvement in PFS compared with historical values. Median PFS and OS were 8.3 mo (95%CI: 5.5-9.9) and 12.3 mo (95%CI: 11.3-17.2), respectively. The chemotherapy toxicity did not increase, but bevacizumab-related toxicities were detected (grade 3 hypertension: 28%, gastric perforation: 6%, myocardial infarction: 2%). The study concluded that the addition of bevacizumab to chemotherapy improved the response rate, PFS, and OS by 75% compared with historical controls[68]. In a another phase Ⅱ trial, previously untreated patients with advanced gastroesophageal disease received bevacizumab 7.5 mg/kg in combination with docetaxel (70 mg/m^2) and oxaliplatin (75 mg/m^2) on day 1 of each cycle. Thirty eight patients were included in this study. Complete, partial, and stable responses were detected in 5%, 37%, and 37% of patients, respectively. Median PFS and OS were 6.6 mo and 11.1 mo. The most common serious side effect was neutropenia detected in 34% of patients. The most important bevacizumab-related side effect was gastrointestinal perforation reported in 8% of patients. The addition of bevacizumab to docetaxel and oxaliplatin had promising activity[69]. The response rate of combination therapy of bevacizumab with modified docetaxel/cisplatin and fluorouracil chemotherapy was 67% (95%CI: 50%-81%). A total of 44 patients were enrolled in this study. The median PFS was 12 mo (95%CI: 8.8-18.2). The median OS was 16.8 mo (95%CI: 12.1-26.1) and 2-year survival was 37%. In this phase Ⅱ trial, bevacizumab in combination with mDCF showed marked efficacy in patients with advanced gastroesophageal cancer[70]. Bevacizumab (15 mg/kg) was also evaluated in combination with capecitabine 850 mg/m^2 BID on days 1-14, and oxaliplatin 130 mg/m^2 on day 1 of a 21-d cycle, in patients with advanced gastroesophageal cancer. The median PFS and OS were 7.2 mo and 10.8 mo, respectively. Response rate was 51.4%. The regimen was well tolerated with favorable activity in advanced stage gastroesophageal cancer[71]. Following these phase Ⅱ trials, a phase Ⅲ trial of bevacizumab in combination with cisplatin and fluoropyrimidines was conducted in patients with AGC. Patients received bevacizumab 7.5 mg/kg or placebo followed by cisplatin 80 mg/m^2 on day 1 plus capecitabine 1000 mg/m^2 twice daily for 14 d or fluorouracil infusion, every 3 wk. The patients received cisplatin for 6 cycles and fluoropyrimidines and bevacizumab until progression. The primary endpoint was OS. A total of 774 patients were enrolled in the study and randomized to bevacizumab plus chemotherapy or chemotherapy alone. The median OS was 12.1 and 10.1, respectively (HR = 0.87; 95%CI: 0.73-1.03, P = 0.10). In the bevacizumab group, the median PFS was 6.7 mo compared with 5.3 mo in the chemotherapy alone group (HR = 0.80; 95%CI: 0.68-0.93, P = 0.0037). The response rate was significantly improved in the bevacizumab group compared with the chemotherapy alone group (46.0% *vs* 37.4%; P = 0.0315). In the bevacizumab plus chemotherapy and chemotherapy alone groups, the most common serious side effects were neutropenia (35% *vs* 37%), anemia (10% *vs* 14%), and decreased appetite (8% *vs* 11%). In first-line treatment of advanced stage gastric cancer, bevacizumab in combination with chemotherapy improved PFS and response rate compared with chemotherapy alone. However, this trial was insufficient to meet its primary endpoint[72]. In another phase Ⅲ trial, the authors hypothesized that geographic differences might have affected the results of the AVAGAST trial and they performed the same study in Chinese patients. A total of 202 patients were randomized to receive bevacizumab plus cisplatin-capecitabine regimen or capecitabine-cisplatin combination alone. The median OS and PFS were similar in the two treatment groups[73].

Monoclonal antibody against VEGFR

In the literature, it was reported that the VEGF-A, which is the main moderator of angiogenesis act on VEGF receptor-2 (VEGFR2), is essential for tumor

angiogenesis[74]. Ramucirumab is a humanized Ig G1 monoclonal antibody directed against to extracellular VEGF binding domain of VEGFR2 and blocks receptor activation of VEGFR2[75]. In a phase Ⅰ trial of ramucirumab, 37 patients with solid organ malignancies were treated with 2 to 16 mg/kg of ramucirumab. Fifteen of 37 patients (40%) had either a partial response or stable disease. Among the evaluable patients, tumor perfusion and vascularity decreased in 69%. In this phase Ⅰ trial, a wide range of ramucirumab doses showed antitumor activity and antiangiogenic effects[76]. This study showed that ramucirumab may be potential therapy for cancers in which VEGFR2 plays a crucial role in tumor progression. Afterwards, a phase Ⅲ randomized double blind trial of ramucirumab was conducted in patients with advanced gastroesophageal cancer as second-line therapy at 119 centers in 29 countries. The patients with advanced gastroesophageal cancer who progressed after first-line platinum-containing or fluoropyrimidine-containing chemotherapy, were included in the study. A total of 355 patients were randomized 2:1 to receive ramucirumab (8 mg/kg, iv) plus best supportive care (n = 238) or placebo plus best supportive care (n = 117) every 2 wk until progression or unacceptable toxicity or death. The primary endpoint of the REGARD study was OS. In the ramucirumab group, the median OS was 5.2 mo (IQR: 2.3-9.9) compared with 3.8 mo (1.7-7.1) in those receiving placebo (HR = 0.776; 95%CI: 0.603-0.998, P = 0.047). For ramucirumab and placebo groups, the median PFS was 2.1 and 1.3 mo (HR = 0.483; 95%CI: 0.376-0.620, P < 0.001). The objective response rate in ramucirumab and placebo groups was 3.4% and 2.6%, respectively. Hypertension occurred more often in the ramucirumab group compared with the placebo group (16% *vs* 8%) and other adverse event rates were similar between the groups. Ramucirumab was the first targeted therapy acting as a single agent in patients with advanced gastroesophageal cancers[77]. The RAINBOW study is another phase Ⅲ randomized, placebo-controlled, double-blind study conducted in 170 centers in 27 countries. In this study 665 patients with advanced gastroesophageal adenocarcinoma were randomized in a 1:1 ratio to receive ramucirumab 8 mg/kg (n = 330) or placebo (n = 335) intravenously biweekly plus weekly paclitaxel 80 mg/m^2 intravenously in a 28-d cycle. The study enrolled patients who had locally advanced gastric or gastroesophageal junction adenocarcinoma, and determined the objective radiological or clinical disease progression during or within 4 mo of the last dose of first-line platinum and fluoropyrimidine doublet with or without anthracycline. In patients receiving ramucirumab plus paclitaxel, OS was significantly higher compared to patients receiving paclitaxel plus placebo (median OS: 9.6 mo, 95%CI: 8.5-10.8 *vs* 7.4 mo, 95%CI: 6.3-8.4; HR = 0.807; 95%CI: 0.678-0.962, P = 0.017). The median PFS in the groups receiving ramucirumab plus paclitaxel and paclitaxel plus placebo was 4.4 mo (95%CI: 4.2-5.3) and 2.9 mo (95%CI: 2.8-3.0), respectively (HR = 0.635; 95%CI: 0.536-0.752, P < 0.0001). In the ramucirumab group, the median duration of treatment was 18 wk (IQR: 10.0-31.1) compared with 12 wk (6.4-20.0) in those receiving paclitaxel with placebo. The incidence of grade 3 or higher side effects was higher in the ramucirumab plus paclitaxel group compared with the paclitaxel plus placebo group. These side effects were neutropenia (41% *vs* 19%), leucopenia (17% *vs* 7%), hypertension (14% *vs* 2%), abdominal pain (6% *vs* 3%), and fatigue (12% *vs* 5%). In patients with advanced stage gastroesophageal cancer who failed first-line therapy, the median PFS and OS was significantly increased with addition of ramucirumab to paclitaxel compared with paclitaxel alone[6]. In April 2014, the FDA approved ramucirumab as a single agent for the treatment of patients with advanced gastroesophageal adenocarcinoma and disease progression during or after prior treatment with fluoropyrimidine- or platinum-containing chemotherapy. Seven months later in November 2014, based on the results of the RAINBOW study, the FDA approved ramucirumab in combination with paclitaxel for advanced gastric or gastroesophageal cancer patients who progressed after first-line platinum plus fluoropyrimidine with or without an anthracycline chemotherapy (Tables 1 and 2).

VEGFR TK inhibitors

Sunitinib is a small orally potent multi-TK inhibitor which blocks the TK domains of VEGF and, platelet derived growth factor receptor (PDGFR)[78]. In a phase Ⅰ study, sunitinib in combination with capecitabine/oxaliplatin had an acceptable safety profile in patients with AGC. In this phase Ⅰ study, the median PFS of sunitinitib in combination with capecitabine/oxaliplatin therapy was 7.6 mo (95%CI: 5.0-8.4)[79]. In 2011, sunitinib was evaluated as a second-line single agent therapy for patients with advanced gastric cancer who had received prior chemotherapy. A total of 78 patients were enrolled in this phase Ⅱ trial, and patients received sunitinib 50 mg/d (4 wk on treatment, followed by 2 wk off treatment). A partial and stable response was detected in 2 (2.6%) and 25 (32.1%) patients, respectively. Median PFS and OS was 2.3 mo (95%CI: 1.6-2.6) and 6.8 mo (95%CI: 4.4-9.6), respectively. The most important grade 3 or more serious side effects were thrombocytopenia and neutropenia which were reported in 34.6% and 29.4% of patients, respectively[80]. This study showed that sunitinib has an insufficient effect as a single agent for patients with AGC. In an another open-label phase Ⅱ trial, sunitinib in combination with docetaxel (sunitinib 37.5 mg and docetaxel 60 mg/m^2) was compared with single agent docetaxel (60 mg/m^2, every 3 wk) in patients with AGC as second-line therapy. A total of 107 patients were enrolled and randomized to a combination of

sunitinib and docetaxel or single agent docetaxel. The median PFS was 3.9 mo (95%CI: 2.9-4.9) and 2.6 mo (95%CI: 1.8-3.5), respectively, and the difference was not significant (P = 0.206). However, the objective response rate was significantly higher in the combination arm (1.1% *vs* 14.3%, P = 0.002). The addition of sunitinib to docetaxel as second-line therapy in patients with AGC did not improve PFS, but increased the objective response rate[81].

Apatinib is an oral, highly potent TK inhibitor targeting VEGFR2. In a phase Ⅱ trial, patients with metastatic gastric cancer who did not respond to two lines of chemotherapy regimens were randomized to receive placebo (group A), apatinib 850 mg once daily (group B), or apatinib 425 mg BID (group C). A total of 144 patients were enrolled and randomized to three groups. The OS was 2.50 mo (95%CI: 1.87-3.70), 4.83 mo (95%CI: 4.03-5.97), and 4.27 mo (95%CI: 3.83-4.77), respectively. PFS was 1.40 mo (95%CI: 1.20-1.83), 3.67 mo (95%CI: 2.17-6.80), and 3.20 mo (95%CI: 2.37-4.53), respectively. The differences between OS and PFS between the apatinib and placebo group were statiscally significant (P < 0.001). In the apatinib groups the most common serious adverse events were hand-foot syndrome and hypertension. In this phase Ⅱ trial, apatinib showed activity in patients with AGC who had progressed after two lines of chemotherapy[82] (Figure 1).

MET INHIBITORS

c-Met is a protein TK encoded by proto oncogene Met. c-Met protein TK is activated by its ligand hepatocyte growth factor receptor (HGFR). c-Met is overexpressed and mutated in a variety of malignancies[83]. During wound healing and embryonic development c-Met activity is crucial. However, multiple mechanisms such as HGF stimulation, gene amplification or mutation, and cross-talk with other receptors could overactivate c-Met kinase. c-Met is activated *via* its natural ligand HGFR. Activation of c-Met results in angiogenesis, proliferation, migration, invasion, and metastasis of tumors. c-Met aberrant expression was found in gastric carcinoma cell lines[84]. In one study, 43 gastric carcinoma patients, were evaluated for expression of c-Met and HGF genes and mutations in the kinase domain of the Met gene. Met and HGF protein were expressed in 29 (67%) and 22 (51%) of these patients, respectively[85]. Gene amplification was detected in 10.2% of patients with gastric carcinoma and was associated with depth of tumor invasion and lymph node metastasis[86]. In a meta-analysis, the prognostic significance of c-Met amplification and expression was evaluated in 2258 patients with gastric cancer. It was demonstrated that c-Met amplification had an unfavorable impact on OS of patients with gastric cancer (HR = 2.57; 95%CI: 1.97-3.35)[87]. Activated Met sends signals through RAS-mitogen activated protein kinase (RAS-MAPK) and phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K-Akt) pathways to initiate cellular processes including motility, survival, proliferation, morphogenesis, and angiogenesis[88]. A recent retrospective study showed Met overexpression in 4%-63% of gastric tumor tissues[89]. On the other hand, *Met* gene amplification was demonstrated in up to 5% of treatment-naive patients with gastric cancer[90]. Two types of c-Met inhibitors are described. These are monoclonal antibodies and small molecules inhibiting the enzymatic TK activity of cMet.

Monoclonal antibodies blocking HGF-cMet pathway

Rilotumumab (AMG 102) is a fully human monoclonal IgG2 antibody that binds HGF, prevents its binding to the Met TK receptor, and prevents activation of MET TK and downsignaling. Rilotumumab was evaluated in a phase 1 trial in patients with refractory solid tumors. Total 40 patients were enrolled into six dose escalation groups (0.5, 1, 3, 5, 10, or 20 mg/kg AMG 102 i.v. every 2 wk). Twenty three patients were evaluable for the treatment response and 16 had a best response of stable disease with PFS ranging from 7.9-40 wk. AMG 102-related side effects were fatigue (13%), constipation (8%), nausea (8%), vomiting (5%), anorexia (5%), myalgia (5%), and hypertension (5%)[91]. In a phase 1b and Ⅱ study, rilotumumab in combination with epirubicin, cisplatin, and capecitabine (ECX) was tested as first-line therapy in patients with advanced gastric or esophagogastric junction cancer. In the phase 1b part of the study, a safe dose of rilotumumab in combination with ECX was identified. In the phase Ⅱ part of the study, 121 patients were randomly assigned to receive rilotumumab 15 mg/kg plus ECX (n = 40); rilotumumab 7.5 mg/kg plus ECX (n = 42) or placebo plus ECX (n = 39). PFS was 5.1 mo (95%CI: 2.9-7.0), 6.8 mo (4.5-7.5) and 4.2 mo (2.9-4.9), respectively. The HR for the PFS in the rilotumumab 15 mg/kg and 7.5 mg/kg groups compared with the placebo group was 0.69 (80%CI: 0.49-0.97; P = 0.164) and 0.53 (80%CI: 0.38-0.73; P = 0.009), respectively. Adverse events detected more frequently compared with placebo group were neutropenia (in combined rilotumumab group: 54% *vs* placebo: 33%), anemia (40% *vs* 28%); thrombocytopenia (11% *vs* none), peripheral edema (27% *vs* 8%), and venous thromboembolism (20% *vs* 13%). Serious adverse events were more common in the rilotumumab group compared with the placebo group (neutropenia 44% *vs* 28% and venous thromboembolism 20% *vs* 10%). This phase Ⅱ trial showed that addition of rilotumumab to ECX had greater activity compared with ECX alone and had a tolerable safety profile[92]. In a biomarker study of this phase Ⅱ study, tumor and plasma samples were evaluated for Met protein levels and gene copy numbers to identify any subgroup of patients who might benefit from rilotumumab. Tumor samples were

available for 62 patients in the rilotumumab 15 mg/kg and 7.5 mg/kg groups and 28 patients in the placebo group. In both rilotumumab groups, if more than 50% of tumors stained positive for Met this subgroup was defined as Met-high. The median OS for the Met-high group was 11.1 mo (80%CI: 9.2-13.3) compared with 5.7 mo (80%CI: 4.5-10.4) in the placebo group (HR = 0.29; 95%CI: 0.11-0.76, P = 0.012). On the other hand, in the rilotumumab group, the OS of Met-low patients (tumor cells < 50% positive) compared with the placebo group was not significantly different (HR = 1.84; 95%CI: 0.78-4.34). In the chemotherapy alone group, the Met-high subpopulation had a poor prognosis and shorter OS compared with the Met-low subpopulation (HR = 3.22; 95%CI: 1.08-9.63). In this study, the gene copy number of Met and plasma levels of soluble Met protein were not associated with PFS or OS. In patients receiving rilotumumab plus ECX, high staining rate (> 50%) of Met protein by immunohistochemistry was the predictor of response to rilotumumab therapy. In the ECX alone group, the subpopulation of patients with high (> 50%) Met staining had a poor prognosis[93].

In the RILOMET-1 study, planned 450 patients with advanced c-met positive gastric or GEJ cancer will be randomized to receive either ECX (epirubicin 50 mg/m^2 and 60 mg/m^2 on day 1, and oral capecitabine 625 mg/m^2 twice daily on days 1-21) plus rilotumumab 15 mg/kg or placebo repeated every 3 wk. This study is ongoing, but not recruiting participants. It is estimated to complete the analyzes in March 2017[94].

An ongoing randomized phase Ⅲ trial of rilotumumab in combination with cisplatin and capecitabine as first-line therapy for patients with advanced MET-positive gastric or gastroesophageal junction tumors plans to include 450 patients in the study population[95].

Onartuzumab is a monoclonal antibody which binds to the Met receptor and prevents the binding of HGF and activation of Met TKs[96]. In a phase 1 study, onartuzumab alone and in combination with bevacizumab was well tolerated. In this phase 1 study, one patient with solitary hepatic metastasis of gastric cancer showed a complete response following four cycles of treatment with single-agent onartuzumab (20 mg/kg)[97].

In an ongoing phase Ⅲ trail, onartuzumab in combination with mFOLFOX6 regimen in patients with HER2-negative and Met-positive AGC as first-line therapy was evaluated. Patients were randomized to receive either mFOLFOX plus onartuzumab or placebo. mFOLFOX was planned to be administered for up to 12 cycles; onartuzumab and placebo was planned to be administered up to progression[98].

c-Met TK inhibitors

Tivantinib is a small molecule orally administered and a potent inhibitor of c-Met kinase. Tivantinib was tested in a phase Ⅰ study in patients with refractory solid organ malignancies. A partial or stable response was achieved in 3 patients (3.8%) and 40 patients (50.6%), respectively. Grade 3 or more toxicity related to tivantinib was detected in two patients. In a phase 1 study, tivantinib 360 mg BID was well tolerated in patients with refractory advanced solid tumors[99]. In a phase Ⅱ trial, tivantinib monotherapy was evaluated in Asian patients with AGC who were previously treated (1 or 2 lines of therapy). Tivantinib 360 mg orally BID was administered to 30 patients. No objective response was detected and the disease control rate was 36.7% (11/30 patients). Median PFS was 43 d (95%CI: 29.0-92.0). Serious side effects were observed in 13 patients (43.3%). In 4 (13.3%) patients c-Met gene amplification (≥ 5 copies/cell) was observed. In this phase Ⅱ trial, tivantinib monotherapy showed modest activity in previously treated Asian patients with AGC[100].

Crizitonib is a small molecule orally administered and targets both c-Met and anaplastic lymphoma kinase TKs. In an expanded phase 1 cohort study, 489 patients with advanced gastroesophageal cancers were analyzed for Met, EGFR, and HER2 amplification status. In this study, four patients with Met-amplified tumors were treated with crizitonib (5%; n = 4 of 80), and two had tumor shrinkage (-30% and -16%); the PFS of the two patients was 3.7 and 3.5 mo. This study concluded that c-Met-amplified gastroesophageal cancers were highly aggressive and responsive to crizitonib therapy[101] (Figure 1).

MAMMALIAN TARGET OF RAPAMYCIN INHIBITORS

Mammalian target of rapamycin (mTOR) is closely related to MAPK, and is a key regulator of cellular growth, proliferation, and angiogenesis[102]. Mutation of gene locations of proteins related to these pathways resulting in aberrant activation of mTOR pathway[103]. The mTOR pathway is activated in patients with gastric cancer, and could be a possible target for therapy[104]. The proteins involved downstream in the mTOR pathway, including eIF4E and 4E binding proteins, were shown to be increased in gastric cancer cell lines[103]. Everolimus (RAD001) is an oral inhibitor of the mTOR pathway, reducing phosphorylation of 4E-BP1 protein and production of proangiogenic factors such as hypoxia-induced factor alpha and VEGF in gastric tumor cell lines[105]. In gastric cancer xenograft models, everolimus significantly inhibited tumor growth[106]. In a phase Ⅰ study of everolimus in patients with solid malignancies, nine patients were included. One patient with gastric cancer receiving 10 mg RAD001 daily showed a marked response to therapy[107]. In another phase Ⅰ trial, everolimus was evaluated in combination with capecitabine in patients with AGC. After a median follow-up of 5.6 mo (range, 2.3-8.1), median PFS was 1.8 mo (95%CI: 0.8-2.8). The sum of the widest tumor diameters was decreased in 28.7% of the patients. Dose-limiting serious toxicities were

infection, mucositis, hyperglycemia, and hyponatremia. The suggested dose of capecitabine in combination with everolimus was 650 mg/m^2 BID and 5 mg BID, respectively[108]. In a phase Ⅱ trial of everolimus (2 mg/daily × 5 mg/daily, 1-21 d) with capecitabine (2 mg/daily × 650 mg/daily, 1-14 d), 57 patients were enrolled and 43 patients were evaluable for response. Five achieved a partial response, 18 showed stable disease, and the disease control rate was 48.9% (95%CI: 34.6%-63.2%). The median PFS and OS were 11.0 wk (95%CI: 5.7-16.3) and 21.0 wk (95%CI: 14.3-27.7), respectively. Serious nausea, diarrhea, and stomatitis occurred in 2, 3, and 3 patients, respectively. In pretreated gastric cancer patients the combination of capecitabine with everolimus was shown to be effective[109].

In a phase Ⅱ trial of everolimus in 53 patients with AGC who were previously treated with chemotherapy, the primary endpoint was disease control rate. Patients received 10 mg everolimus daily orally until disease progression or study discontinuation. None of the patients had a complete or partial response. However, tumor size was decreased in 45% of patients. The disease control rate was 56.0% (95%CI: 41.3%-70.0%). The median PFS and OS were 2.7 mo (95%CI: 1.6-3.0) and 10.1 mo (95%CI: 6.5-12.1), respectively. Common serious toxic effects of everolimus were anemia, hyponatremia, increased gamma-glutamyl transferase, and lymphopenia. Mild pneumonitis was detected in 15.1% of patients. In this phase Ⅱ trial, single agent everolimus had favorable efficacy in patients with AGC[110]. Following the encouraging results of everolimus in phase Ⅱ trials, the double blind, randomized phase Ⅲ Granite-1 study was conducted in patients with AGC who had progressed after 1 or 2 lines of therapy. Patients were randomly assigned to receive everolimus 10 mg/daily or placebo with best supportive care in a 2:1 ratio. The primary endpoint of study was OS. The study population included 656 patients. In the everolimus group, the median OS was 5.4 mo compared with 4.3 mo in those receiving placebo (HR = 0.90; 95%CI: 0.75-1.08, P = 0.124). In the everolimus and placebo groups, median PFS was 1.7 mo and 1.4 mo, respectively (HR = 0.66, 95%CI: 0.56-0.78, P < 0.01). The most frequently observed adverse events were anemia, decreased appetite, and fatigue. In patients with AGC who progressed after first- or second-line chemotherapy, single agent everolimus did not improve OS[111] (Figure 1).

OTHER TARGETED AGENTS

Fibroblast growth factor receptor

In preclinical gastric cancer cell studies, it was demonstrated that fibroblast growth factor receptor (FGFR)2 amplification was associated with increased tumour cell proliferation and survival. In gastric cancer xenograft models, amplified FGFR2 was associated with high tumor grade (P = 0.034)[112]. In a multicenter international trial, FGFR2 FISH was performed on tumor samples of 961 patients with gastric cancer. The FGFR2 positivity and association between clinicopathological features were analyzed. The FISH positivity rate of patients from the United Kingdom, China, and South Korea were 7.4%, 4.6%, and 4.2%, respectively (P > 0.05). FGFR2 amplification was associated with lymph node metastases (P < 0.0001) and poor OS (P = 0.007). This study showed that in patients with gastric cancer, FGFR2 amplification is associated with poor prognosis[113]. FGFR2 may be a novel target for treatment of patients with AGC.

Tetrapsanin family

Tetraspanins belong to a family of cell surface-associated proteins which play a major role in the immune system, cell survival, proliferation, adhesion, migration, and tumor invasion[114]. CD9 a novel protein which is a member of tetraspanin family[115]. In a study, CD9 expression of tissues from 78 AGC patients was compared with normal tissues. It has been demonstrated that CD9 expression was more prominent than in normal tissues[116]. In gastric cell lines, anti-CD-9 monoclonal antibody significantly suppressed tumor growth, increased apoptosis, and inhibited angiogenesis[117].

Claudins

Claudins are a family of proteins including 27 proteins playing a major role in selective permeability of cellular tight junctions[118]. Claudins may have a role in gastric carcinogenesis and progression of gastric tumors. One study demonstrated that the claudin-18 splice variant 2 is a suitable target for therapeutic antibody development against gastric cancer[119]. After that, claudiximab, a chimeric monoclonal antibody against claudin 18.2 was developed. In a phase Ⅱ trial, patients with advanced gastroesophageal cancer and positive staining for claudin 18.2 by immunohistochemistry were enrolled. The patients received claudiximab until disease progression. A total of 31 patients were evaluated for tumor response. A partial response and stable disease were demonstrated in 4 and 8 patients (ORR: 13%, disease control rate: 39%). The most frequent grade 3 adverse events were vomiting (8.24%), nausea (4.12%), and hypersensitivity (1.3%)[120]. In a phase Ⅱ trial, the benefit of addition of claudiximab to a chemotherapy regimen is being tested. Patients with claudin 18.2 positive adenocarcinoma of gastric cancer were randomized to receive claudiximab plus EOX (Epirubicin/oxaliplatin/capecitabine) or EOX alone as first-line therapy (NCT01630083).

Immunotherapy

Immunologic checkpoint blockade with antibodies against different T cell regulatory mechanisms, including cyctotoxic T lymphocyte antigen (CTLA4),

Table 3 Ongoing Phase Ⅱ and Ⅲ studies

Target	Agents	Trial number	Setting	Phase	Primary end point	Status
HER-2	Arm A: pertuzumab + trastuzumab + cisplatin + fluoropyrimidine *vs* Arm B: placebo + trastuzumab + cisplatin + fluoropyrimidine	NCT01774786	First line	Ⅲ	OS	Recruiting
HER-2	Arm A: Docetaxel or paclitaxel Arm B: T-DM1 3.6 mg/kg every 3 wk Arm C: T-DM1 2.4 mg/kg once a week	NCT01641939	First line	Ⅱ / Ⅲ	Phase Ⅱ: Dose of TDM-1 Phase Ⅲ: OS	Recruiting
HER-3	Arm A: MM-111 + Paclitaxel + Trastuzumab Arm B: Paclitaxel + Trastuzumab	NCT01774851	⩾ Second line	Ⅱ	PFS	Active, not recruiting
MET	Arm A: Rilotumumab 15 mg/kg plus ECX Arm B: Placebo plus ECX	NCT01697072	First line	Ⅲ	OS	Active, not recruiting
MET	Arm A: onartuzumab plus mFOLFOX6 Aram B: placebo plus mFOLFOX6	NCT01662869	First line	Ⅲ	OS	Active, not recruiting
CTLA4	Arm A: Ipilimumab Arm B: Best Supportive Care	NCT01585987	Maintanence	Ⅱ	PFS	Active, not recruiting
PD-1	Arm A: Nivolumab (ONO-4538) Arm B: Placebo	NCT02267343	⩾ Second line	Ⅲ	OS	Recruiting

CTLA4: Cytotoxic T lymphocyte antigen; PD-1: Programmed cell death.

the programmed cell death protein-1 (PD-1) or its ligand (PD-L1), is an effective method for reversing cancer immunosuppression and thereby activating anti-tumor immunity against several different cancer types[121,122]. CTLA4 was the first negative immune checkpoint molecule to be targeted by monoclonal antibodies. Following the activation of T cells, CTLA4 is upregulated on the activated T cells and blocks further stimulation by the co-stimulatory molecule CD28. Therefore, CTLA4 has a negative effect on activated T cells and blocks further activation[123]. In a previous study, in patients with melanoma antibody against CTLA4 showed T cell activation[124]. In a phase Ⅱ trial, the efficacy of tremelimumab, which was a monoclonal antibody targeting CTLA4, was evaluated as second-line therapy in patients with advanced gastric and esophageal adenocarcinomas. Eighteen patients were enrolled to in the. Tremelimumab was given every 3 mo until symptomatic disease progression. Four patients had stable disease and one patient achieved a partial response after eight cycles of therapy. The response rate of tremelimumab was low in patients with advanced gastroesophageal carcinoma[125]. In a randomized, open-label, two-arm, phase Ⅱ trial, ipilimumab maintenance will be tested in patients with advanced gastroesophagel cancer who did not have progressive disease following first-line fluoropyrimdine and platin chemotherapy. The study plans to randomize 114 patients to ipilimumab maintenance arm and best supportive care arms[126].

PD-1 protein, a T cell co-inhibitory receptor, and one of its ligands, PD-L1, play a pivotal role in the ability of tumor cells to evade the host's immune system. In a preclinical study, expression of PD-L1 was found in human gastric carcinoma specimens but not in normal or gastric adenoma tissues[127]. In 2012, a phase Ⅰ trial of intravenous anti-PD-L1 antibody in patients with advanced cancers was reported. This phase Ⅰ study also included seven patients with AGC. None of the patients with gastric cancer demonstrated a partial or complete response[121].

Nivolumab, a fully human IgG4 PD-1 blocking antibody in combination with ipilimumab or as a single agent is being tested in an ongoing phase Ⅰ/Ⅱ trial in patients with solid malignancies, including patients with gastric cancers[128]. In a phase Ⅲ trial, nivolumab is also being evaluated in patients with advanced gastroesophageal cancers as second- or third-line therapy (NCT02267343).

Insulin-like growth factor inhibitors

Insulin-like growth factor Ⅰ (IGF-1) promotes growth of gastric cancer cells[129]. IGF receptor type Ⅰ (IGF-IR) expression is associated with poor OS in patients with AGC. In a study of 87 tumor specimens, 67 (77%) showed IGF-IR expression (defined as > 10% membranous staining). Multivariate survival analysis showed that IGF-IR-positivity (HR = 2.14; 95%CI: 1.20-3.82, P = 0.01) was a predictor of poor outcome[130].

In a phase Ⅰ trial, ganitumab (AMG 479) was tested in 19 patients including three patients with AGC. The most common serious (grade ⩾ 3) adverse events were neutropenia (21%), leukopenia (16%), and lymphopenia (11%). Stable disease was observed in seven patients[131].

Heat shock protein inhibitors

Heat shock protein 90 (HSP90) is highly expressed in cancer tissues. In tumor samples of 322 patients with gastric cancer, 69.6% demonstrated positive expression of HSP90. HSP90 protein expression was significantly associated with depth of invasion (P < 0.001), lymph node metastasis (P < 0.001), and stage

of disease ($P < 0.001$). This study reported that HSP90 expression is an independent prognostc indicator of poor PFS and OS in patients with gastric cancer[132]. A second generation HSP90 inhibitor increased apoptosis in gastric cell lines[133]. Single agent efficacy of an HSP inhibitor was demonstrated in a phase Ⅰ trial[134]. Ganetespib is a novel triazolone heterocyclic inhibitor of HSP90 and is a biologically rational treatment strategy for advanced esophagogastric cancers. In a single arm phase Ⅱ trial, 26 patients with advanced gastroesophageal cancer received ganetespib 200 mg/m^2 i.v. on days 1, 8, and 15 of a 28-d cycle as second- or third-line therapy. The most common serious adverse events were; leucopenia (12%), fatigue (12%), diarrhea (8%), and elevated alkaline phosphatase (8%). A complete response was detected in one patient. The ORR was 4%. The median PFS and OS was 1.6 mo and 2.8 mo, respectively. The study was terminated early due to insufficient efficacy of single agent ganetespib[135].

CONCLUSION

Trastuzumab was the first molecule shown to prolong both PFS and OS in patients with AGC when added to first-line chemotherapy. In April 2014, the FDA approved ramucirumab as a single agent for the treatment of patients with advanced gastroesophageal adenocarcinoma with disease progression during or after prior treatment with fluoropyrimidine- or platinum-containing chemotherapy. In November 2014, based on results of the RAINBOW study, the FDA approve ramucirumab in combination with paclitaxel for advanced gastric or gastroesophageal cancer patients who progressed after first-line platinum plus fluoropyrimidine with or without an anthracycline. The two targeted agents are in clinical use for patients with AGC (Table 1). Many phase Ⅱ-Ⅲ clinical trials failed to showed an effect of different targeted agents for patients with AGC (Tables 1 and 2). On the other hand, some of the molecules have shown promising effects in phase Ⅱ trials and are expected to be in use presently. The pertuzumab and c-Met pathway inhibitors showed modest effects in phase Ⅱ trials. The results of two important ongoing phase Ⅲ trials (JACOB and RILOMET-1) may change the suggested first-line treatment options in patients with AGC (Table 3).

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